Exhibit A

Docket No.: 0656-032US3A

IN THE UNITED STATED PATENT AND TRADEMARK OFFICE

Applicant: Salter et al.

U.S. Serial No. 10/578,935

Examiner: Gitomer, Ralph

Art Unit: 1651

Title: INHIBITION ASSAY METHOD AND DEVICE FOR DETECTION OF ANTIBIOTICS

DECLARATION OF ROBERT S. SALTER UNDER 37 C.F.R. §1.132

I declare:

1. I have been employed at Charm Sciences, Inc., the assignee of the above-captioned patent application, since 1982. I have held several positions at Charm Sciences including Plant Manager and Vice President of Regulatory Affairs and Industrial Service. I currently hold the position of Vice President, Regulatory & Industrial Affairs. I also consistently spend a significant portion of my working hours in new product research and development.

2. I have published extensively in the field of antibiotic, alkaline phosphatase, allergen, and microbial detection. Attached, as Exhibit 1 hereto, is my curriculum vitae which lists over three dozen publications in this scientific area of which I am author or a co-author.

3. In addition to product development and manufacture, during the past nineteen years I have been responsible for gaining industry approval, on behalf of Charm Sciences, of more than fifteen food safety diagnostic tests including twelve for the detection of antibiotics in milk. Those industry approvals included evaluation by the Food and Drug Administration (FDA) and approval by the Interstate Conference of Milk Shippers (NCIMS) and the American Association of Analytic Chemist Research Institute (AOAC Research Institute), Environmental Protection Agency (EPA) and the Food Safety Inspection Service of the US Department of Agriculture (FSIS).

4. I am the United States International Dairy Federation (IDF) appointed representative on the IDF Standing Committee for Analytical Methods for Additives and Contaminates. I am also Chair of the IDF/ISO (International Standards Organization) Standing Committee on Minor Components and Characterization of Physical Properties. In that role, I am one of six international representatives in the IDF/ISO Methods Standards Steering Group that advise methods and standards to CODEX committees.

5. An important aspect of test kit development and approval, particularly for antibiotic detection tests, is for the test to meet industry and regulatory requirements for sensitivity. My experience in developing, manufacturing, and gaining approval of tests to detect antibiotics that meet U.S. requirements (safe levels), and European requirements (MRL levels), is extensive.

6. As a result of my experience and education, I am an expert in tests that detect antibiotics in foods including milk and tissue. I am also an expert in specific drug sensitivities and the technologies of detection.

7. I have read the Office Action issued in U.S. Serial No. 10/578,935 on January 28, 2009.

8. I have read Langeveld et al, U.S. Patent No. 6,867,015 (the '015 patent). Referring to column 5, lines 5-10 of the '015 patent, it has been well known, conventional and routine practice to non-specifically alter test sensitivity of microbial growth inhibition tests by making coarse adjustments to various test conditions such as pH. Referring to column 5, lines 11-18, it has been a well known, conventional and routine practice to selectively increase test sensitivity of microbial growth inhibition tests to sulfa drugs by adding trimethorpim, ormethoprim and tetroxoprim. It has also been well-known to add analyte analogs to compete with analyte in a sample and, thereby, make a test less sensitive to a particular antibiotic or antibiotic family.

9. According to the '015 patent, cysteine can be used to reduce test sensitivity to penicillins. The '015 patent, however, provides no description or guidance for one skilled in the art to use cysteine in this manner.

10. I have read "The Reaction of Cysteine and Related Compounds with Penicillins and Cephalosporins", Wagner, Eugene S. and Gorman, Marvin, The Journal of Antibiotics, Vol. XXIV, No. 9, page 647 (1971) (Exhibit 2) and "Effect of L-Cysteine on the Activity of Pencillin Antibiotics Against Clostridium Difficile", Markowitz, Sheldon M. and Williams, Denise S., Antimicrobial Agents and Chemotherapy, Vol. 27, No. 3, Mar. 1985, p. 419-421 (1984) (Exhibit 3). According to those publications, copies of which are attached hereto as exhibits 2 and 3, cysteine inactivates the penicillin category of

beta-lactams and does not inactivate the cephalosporin category of beta-lactams. This selective activity of cysteine is consistent with the '015 patent's description of cysteine as reducing sensitivity to the penicillins.

11. I have read Detection of Inhibitors in Milk by Microbial Tests. A review. Suhren G., and Heeschen W., Institute for Hygiene, Federal Dairy Research Centre, Kiel, Germany (1996) (Exhibit 4) and agree with the statement on page 3 that "the idea is to have available methods by which a broad variety of antiinfectives are detected with sensitivities which correspond exactly with the demands, as for example with the EU MRL-concept". That statement reflects a longstanding unresolved need in the field for a broad spectrum test, such as a microbial inhibition test, to detect as many antibiotics (anti-infectives) as possible close to the regulatory (MRL for Europe) level.

12. The 36th Joint FAO/Who Expert Committee on Food Additives meeting in 1990 established an MRL level for tetracycline in milk at 100 ppb and an MRL level for cephapirin in milk at 60 ppb. That MRL was approved through the CODEX Alimentarius Commission in 1994.

13. *Bacillus stearothermophilus* (*B.st.)* has long been a bacteria used in microbial growth inhibition tests to detect antibiotics. Relative to the regulatory levels ((for example the MRL for penicillin G is 4 parts per billion (ppb) and the safe level is 5 ppb)), tests using *B.st.* are overly sensitive to, for example, cephapirin (a cephalosporin) as compared to, for example penicillin G (a penicillin). Using cysteine would provide an effect on such test sensitivity that is opposite of that desired as it would make the test even more sensitive to cephapirin relative to other beta-lactams. Cysteine use would, therefore, be detrimental.

14. A reason for reducing sensitivity to all beta-lactams is to allow the test sensitivity to be increased for other drugs, such as tetracyclines, relative to the beta-lactams. Tests, particularly those using *B.st*, typically have detection levels for tetracycline well above 100 ppb (the MRL for tetracycline) and detection levels for most beta-lactams well below the regulatory level. For that reason, it is valuable to be able to reduce sensitivity to all beta-lactams while increasing test sensitivity to other drugs.

15. Historically, adjusting microbial growth inhibition test factors and components to improve sensitivity to tetracycline had the problem of causing undesirable, excessive sensitivity to other beta-lactams including cephapirin. A test which is overly sensitive to beta-lactams can result in rejection of milk tankers that should not be rejected Determination of Non Actionable Positives Associated with Antibiotic Tests, Stanley E.

Charm, Dairy, Food and Environmental Sanitation, Vol. 14, No. 3, Pages 151-154 (March 1994) (Exhibit 5).

16. Claim 1 as amended describes reduction in test sensitivity by competition between a microbial culture, with sensitivity to beta-lactams and other antibiotics, and an extracted microbial receptor with sensitivity to beta-lactams. The microbial receptor that exists in the culture binds to beta-lactam antibiotic in the sample and, thereby, contributes to the growth inhibition of the culture. The extracted microbial receptor is competitive with the culture receptor for beta-lactam binding and does not inhibit culture growth. Such sensitivity adjustment allows for fine sensitivity adjustment to the broad class of drugs to which the extracted microbial receptor is specific. In my opinion, this method is very different from the methods of sensitivity adjustment referred to by the Examiner and described in the prior art.

17. Due to the unpredictable nature of microbial inhibition technology, when I first experimented with adding a microbial receptor to a microbial culture growth inhibition test, I was uncertain it would provide the desired sensitivity adjustment. There were many possible problems. For example, as a protein, the receptor could have acted as a nutrient or otherwise impacted the growth of the culture in an undesirable or unpredictable manner. As a protein it might have degraded, for example, if it was susceptible to proteases produced by the culture. Indeed, in my opinion, the art of developing microbial culture growth inhibition tests can be unpredictable.

18. The ability to adjust such a microbial growth inhibition test in the manner described, and reflected in claim 1, is important. It has often been the case, particularly with broad spectrum tests that detect beta lactams and other antibiotics, that a change of sensitivity for one or more analytes is desired while the sensitivity for another analyte is already satisfactory. For example, inhibition tests have, historically, not detected tetracycline drugs at their MRL levels. Although the chemistry existed to make such tests detect tetracycline at the MRL levels, the result was to make the beta-lactam detection hypersensitive relative to the MRL levels. Although there was this important, long-felt need to adjust microbial inhibition tests in the manner described the problem has, until now, been unresolved.

19. As is evidenced by the information provided herein, in my opinion, there has been a long-felt, unmet need in the art for a simple procedure for adjusting test sensitivity of microbial growth inhibition tests to all beta-lactams.

20. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Robert S. Salter

Date: June 19 2009